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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,772	06/25/1999	WILLEM JAN MARIE VAN DE VEN	702-990278	1485

7590 02/25/2004

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,772	VAN DE VEN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,29,32-48 and 50-52* is/are pending in the application.

4a) Of the above claim(s) *36-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29,32-35,47,48 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to Applicants response, filed on September 9, 2003. Currently, Claims 28, 29, 32-48 and 50-52 are pending, Claims 36-46 have been withdrawn from consideration, and Claims 28, 29, 32-35, 47-48 and 50-52 are rejected herein. This action contains new rejections necessitated by Applicants' amendments to the claims, and therefore, this action is made FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 28-29, 32-35, 47-48 and 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 28-29, 32-35, 47-48 and 50-52 over "a PLAG1 protein" because it is not clear as to exactly what constitutes "a" PLAG1 protein. The specification does not differentiate between proteins that are considered to be "a PLAG1 protein", and those not considered to be "a PLAG1 protein". For example, it is not clear as to what makes a protein "a PLAG1 protein", or whether a PLAG1 protein can also be characterized as another type of protein.

B) Claims 28-29, 32-35, 47-48 and 50-52 over "the amino acid" and "the sequence translated" because these recitations lack antecedent basis.

C) Claims 28-29, 32-35, 47-48 and 50-52 over "non-physiological proliferative capacity" because it is not clear as to what is encompassed by the recitation of "non-physiological

proliferative capacity". On page 8, lines 13-15, the specification refers to "non-physiological proliferative capacity", but does not define this recitation. Furthermore, this is not an art-recognized term.

D) Claims 32 and 47 over "the PLAG1 fragment" because this recitation lacks antecedent basis.

E) Claims 34, 50 and 52 because it is not clear as to what is meant by "corresponding" to the nucleic acid. It is not clear, as whether this means that the transcript, cDNA, sense or antisense nucleic acid is complementary to the isolated nucleic acid, or has some other type of relationship to the isolated nucleic acid that can be considered to be "corresponding" to the nucleic acid.

F) Claims 48 and 50 over "the promoter region" because this recitation lacks antecedent basis. Furthermore, it is not clear as to what sequence actually encompasses "the promoter region of a CTNNB1 gene".

New Matter

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 28-29, 32-35, 47-48 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants' have amended Claim 28 to recite,

> An isolated nucleic acid *comprising a sequence* encoding *a* PLAG1 protein, wherein the amino acid sequence of the PLAG1 protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116...*or a fragment thereof which can be used to diagnose cells having a non-physiological proliferative capacity*.

(emphasis added). Thus, the claims have been amended to recite that a nucleic acid "comprising 'a' sequence encoding 'a' PLAG1 protein" or a fragment thereof, "which can be used to diagnose cells having a non-physiological proliferative capacity". By using the recitation of "comprising" a sequence encoding "a" PLAG1 protein, the claims encompass any sequence encoding "a" PLAG1 protein or fragment thereof for use in diagnosing cells having a non-physiological proliferative capacity. That is, the claims encompass any sequence that encodes "a" PLAG1 protein or fragment thereof, and any other flanking sequences (because of the use of "comprising") for use in diagnosing cells having a non-physiological proliferative capacity. The specification does not provide such broad support for these claims.

Applicants state, "support for the language 'can be used to diagnose cells having a non-physiological proliferative capacity' is found on page 8, lines 13-15". (see Applicants response page 5) However, this passage does not specify that any sequence that encodes "a" PLAG1 protein or fragment thereof, and any other flanking sequences can be used in diagnosing cells having a non-physiological proliferative capacity. This passage also does not provide support for using "the promoter region of a CTNNB1 gene" or "at least one exon" in diagnosing cells having a non-physiological proliferative capacity (Claims 48 and 51).

6. Claims 28-29, 32-35, 47-48 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The main independent and dependent claims are drawn to:

1) An isolated nucleic acid *comprising a sequence* encoding *a* PLAG1 protein, wherein the amino acid sequence of the PLAG1 protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116...*or a fragment thereof* which can be used to diagnose cells having a non-physiological proliferative capacity.

2) A macromolecule comprising a nucleic acid in isolated form, *comprising a sequence* encoding *a* PLAG1 protein, wherein the amino acid sequence of the PLAG1 protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116...*or a fragment thereof* which can be used to diagnose cells having a non-physiological proliferative capacity.

3) A nucleic acid in isolated form according to claim 28, wherein the amino acid sequence of said PLAG1 fragment *comprises at least one of* the zinc fingers 1 to 7 represented by the sequences as represented in SEQ ID NOS: 117-123.

4) A macromolecule comprising a nucleic acid in isolated form, *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

5) A macromolecule comprising a nucleic acid in isolated form *comprising at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

These claims are broadly drawn to sequences "comprising":

a) *any sequence encoding a* PLAG1 protein (from SEQ ID NO: 116), or *any fragment of* said sequence which can be used to diagnose cells having a non-physiological proliferative capacity;

b) *any* sequence *comprising* at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123);

c) *any* sequence *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity; and

d) *at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

These claims are drawn to as little as a sequence encoding "a" PLAG1 protein (e.g., a sequence encoding a single amino acid found in SEQ ID NO: 116), or fragment thereof (e.g., less than three nucleotides), which can be used to diagnose cells having a non-physiological proliferative capacity. This includes sequences comprising sequences encoding a single PLAG1 protein (or fragment thereof) with any possible flanking sequences (not defined in the specification), sequences from other species, mutated sequences, full-length genes, genomic DNA, and allelic variants having different functional activities than that of the a sequence encoding "a" PLAG1 protein or a fragment thereof (as small as one or two nucleotides), or at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123), or a sequence encoding the promoter region of a CTNNB1 gene, or at least one exon of the CTNNB1 gene. That is, the claims are drawn to a large genus of possible sequences that may have sequences encoding "a" PLAG1 protein (from SEQ ID NO: 116), or a fragment thereof (as small as one or

two nucleotides), or at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123), or a sequence encoding the promoter region of a CTNNB1 gene, or at least one exon of the CTNNB1 gene, embedded therein, which may have different structures and functions from the claimed nucleic acids.

In Figure 4A of the specification, Applicant discloses the cDNA of the nucleotide sequence of the PLAG1 gene (SEQ ID NO: 116), and on page 41 of the specification, Applicant discloses genomic organization of the PLAG1 gene including regulatory regions, i.e. introns, exons, coding and non-coding regions. However, the specification fails to describe nucleic acids "comprising" sequences encoding "a" PLAG1 protein (from SEQ ID NO: 116), or a fragment thereof, or at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123), or a sequence encoding the promoter region of a CTNNB1 gene, or at least one exon of the CTNNB1 gene. With respect to the limitation of "which can be used to diagnose cells having a non-physiological proliferative capacity" the specification does not teach what constitutes or encompasses a "non-physiological proliferative capacity", how the skilled artisan assays for this, any common structures that are associated with this function, or any examples of sequences that have this function.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed* (See page 1117)." (emphasis added)

Additionally, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by

only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, one member of the broadly claimed genus has been defined by structure, i.e., SEQ ID NO: 116. No genomic sequences flanking the nucleic acids encompassed by the claims (see above), sequences from other species, mutated sequences, full-length genes, genomic DNA, and allelic variants having different functional activities than the sequences encompassed by the claims (see above) have been defined by structure. Accordingly, a representative number of species have not been described by their complete structure.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., nucleic acids comprising sequences that have the claimed nucleic acids embedded therein, common structures of the claimed nucleic acids, similar functional domains, description of structures that are similar for use in diagnose cells having a non-physiological proliferative capacity, etc.). In the instant case, no such identifying characteristics have been provided for any of the claimed nucleic acids. Accordingly,

a representative number of species have not been sufficiently described by other relevant identifying characteristics

While at the time of filing, Applicants were in possession of SEQ ID NO: 116, Applicants were not in possession of the broadly claimed genus.

Accordingly, because the specification does make clear that Applicants were in possession of the claimed invention at the time the application was filed, and because the claims are broadly drawn to encompass other nucleic acid molecules not taught or described in the specification, the claims lack adequate written description.

Applicant's attention is also drawn to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1st Paragraph, Written Description Requirement" (published in Federal Register/Vol. 66, No. 4/Friday, January 5, 2001/Notices; p. 1099-1111).

Applicants Arguments

Applicants' argue the specification provides support for the claims because the specification teaches the seven zinc finger domains of PLAG1, exons and the promoter region of CTNNB1, and PCR products of both PLAG1 and CTNNB1, and therefore, there is adequate written description of the claims.

Response to Applicants Arguments

Applicants' arguments have been considered, but are not persuasive for several reasons. First, the claims are drawn to a large genus of possible sequences, which are neither contemplated, nor taught in the specification (see above rejection). Furthermore, the specification does not teach what constitutes or encompasses a "non-physiological proliferative capacity", how the skilled artisan assays for this, any common structures that are associated with

this function, or any examples of sequences that have this function. That is, while the specification teaches examples of using specific probes of the PLAG1 gene (see page 42) for detecting rearrangements of pleomorphic adenoma, the specification does not support the large genus of possible nucleic acids, which can allegedly be used for diagnosing cells having a "non-physiological proliferative capacity". In fact, since pleomorphic adenoma is a tumor of the salivary gland, and a tumor is a tissue that usually results from excessive cell division, it is not clear as to how pleomorphic adenoma cells can be considered to be cells having a "non-physiological proliferative capacity". Accordingly, the rejection is maintained.

7. Claims 28-29, 32-35, and 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the cDNA sequence of the PLAG1 (SEQ ID NO: 116), does not reasonably provide enablement for sequences "comprising":

a) *any sequence encoding a* PLAG1 protein (from SEQ ID NO: 116), or *any fragment of* said sequence which can be used to diagnose cells having a non-physiological proliferative capacity;

b) *any* sequence *comprising* at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123);

c) *any* sequence *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity; and

d) *at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure doe not satisfy the enablement requirement s an whether any necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

I. *Quality of Experimentation Necessary*:

The claimed invention is drawn to sequences "comprising":

a) *any sequence encoding a* PLAG1 protein (from SEQ ID NO: 116), or *any fragment of* said sequence which can be used to diagnose cells having a non-physiological proliferative capacity;

b) *any* sequence *comprising* at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123);

c) *any* sequence *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity; and

d) *at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

At Figure 4A and page 41 of the specification, the Applicant discloses the genomic organization of the PLAG1 gene including regulatory regions, i.e. introns, exons, coding and non-coding regions. Although members of the PLAG1 gene family have been cloned and characterized in the prior art, Applicant fails to describe the nucleic acids encompassed by the

claims. The specification does not disclose any of the sequences comprising the various substitutions, insertions, deletions, allelic variants, different functions, etc. that are encompassed by the claims. Additionally, the specification fails to provide information to enable one of ordinary skill in the art to make or use the claimed nucleic acid using the large number of undisclosed nucleotide variations encompassed by the claims. In the first example, the Applicant discloses directional chromosome walking studies wherein yeast artificial chromosome clones (YACs) are isolated and screened followed by methods of fluorescence *in situ* hybridization for chromosome mapping studies. In the second example and subsequent examples, the Applicant discloses identification of a member of the PLAG1 gene family using classical molecular biology techniques that are well known in the prior art. The examples also disclose wherein probes and primers specific for the PLAG1 gene are utilized in methods of amplification and blotting to detect regions of the PLAG1 gene associated with pleomorphic adenoma. Nowhere in the examples does the Applicant provide information to enable one of ordinary skill in the art to isolate a nucleic acid sequences "comprising":

a) *any sequence encoding a* PLAG1 protein (from SEQ ID NO: 116), or *any fragment of* said sequence which can be used to diagnose cells having a non-physiological proliferative capacity;

b) *any* sequence *comprising* at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123);

c) *any* sequence *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity; and

d) *at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

Furthermore, the specification does not teach what constitutes or encompasses a "non-physiological proliferative capacity", how the skilled artisan assays for this, any common structures that are associated with this function, or any examples of sequences that have this function. In fact, since pleomorphic adenoma is a tumor of the salivary gland, and a tumor is a tissue that usually results from excessive cell division, it is not clear as to how pleomorphic adenoma cells can be considered to be cells having a "non-physiological proliferative capacity".

As to the quality of experimentation required, one of ordinary skill in the art would have to design an experimental procedure to isolate the nucleic acids that are commensurate with the entire scope of the claims.

II. *Amount of Direction and Guidance*

The specification does not provide nucleic acid sequences "comprising":

a) *any sequence encoding a* PLAG1 protein (from SEQ ID NO: 116), or *any fragment of* said sequence which can be used to diagnose cells having a non-physiological proliferative capacity;

b) *any* sequence *comprising* at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123);

c) *any* sequence *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity; and

d) *at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

The examples starting at page 11, lack information concerning how to isolate any of the sequences encompassed by the claims. The examples provided lack information concerning the size and composition of the nucleic acid sequences claimed to be "a PLAG1 protein" or fragment thereof or sequences that can be used in diagnosing cells having a non-physiological proliferative capacity. Since the specification has not adequately identified "a PLAG1 protein" (or fragment thereof) it cannot be determined whether the claimed nucleic acid sequences are indeed considered to be PLAG1 proteins. Therefore, the claimed invention provides insufficient guidance and directions for one skilled in the art to make and use the claimed invention without undue experimentation.

III. *Presence and Absence of Working Examples*

The specification of the claimed invention lacks proper working examples to enable the broadly claimed genus of nucleic acids. Starting on page 11, the specification discloses isolation and analysis of YACs in chromosome walking studies. At page 32, the specification discloses general methods for identifying a member of the PLAG family in salivary glands. At page 53 and 54, Applicant discloses the identification of a PLAG2 gene using classical molecular biology techniques. Beginning at page 56, Applicants discloses a diagnostic test for pleomorphic adenomas of salivary glands using PLAG1-specific primers. At page 59, Applicant discloses a PLAG2 gene as a diagnostic marker for chromosome anomalies. At page 60, Applicant discloses the use of animal models involving PLAG1 as tools in *in vivo* therapeutic drug testing. The examples, however, fail to adequately disclose how to isolate the claimed nucleic acid sequences. Merely making reference to the PLAG1 gene, probes and primers of the PLAG1 gene or PLAG2 gene as a member of the PLAG1 family as being encompassed in the instant

invention does not enable the skilled practitioner to reproduce the results as reported in the specification and isolate the claimed invention.

IV. *Nature of the Invention*

The nature of the invention is nucleic acid sequences "comprising":

a) *any sequence encoding a* PLAG1 protein (from SEQ ID NO: 116), or *any fragment of* said sequence which can be used to diagnose cells having a non-physiological proliferative capacity;

b) *any* sequence *comprising* at least one of the zinc fingers 1 to 7 (represented by SEQ ID NOS: 117-123);

c) *any* sequence *comprising a sequence* encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity; and

d) *at least one* exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

The full scope of the claimed invention is not reproducible due to the lack of guidance presented in the examples beginning at page 11. As noted, the specification does not properly disclose the claimed nucleic acids, how to isolate them, whether and how they can be differentiated from sequences having different function, or what is encompassed by "non-physiological proliferative capacity".

V. *Level of predictability in the art*

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839,

166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In the instant case, the art nor the specification teaches the nucleic acids encompassed by the claims, how to isolate these sequences, any common sequences shared by the claimed nucleic acids, what is considered to be "a PLAG1 protein", or what constitutes or how one assays cells having "non-physiological proliferative capacity".

In order to carry out making and using of the claimed nucleic acids, the experimentation required by the skilled artisan would be considered undue. First, the skilled artisan would have to experiment by altering any of the plurality of possible sequences encompassed by the claims to determine what sequences can be altered, and how they can be altered, and still retain the function of the PLAG1 cDNA of SEQ ID NO: 116. Additionally, once the sequences were obtained, the skilled artisan would have to test the sequences to determine whether the sequences have the specific function of being able to detect pleomorphic adenomas. Furthermore, the skilled artisan would need to experiment to determine what sequences can be used in diagnosing cells having "non-physiological proliferative capacity". Such experimentation requires a large amount of trial and error analysis, with little to no starting point, absent any teaching in the specification (see above), wherein the results of such analysis are unpredictable, and is therefore considered undue.

In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. However, "(I)t is the specification, not the

knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 28 and 33-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Tommerup et al. (Genomics (1995) 27:259-264).

Claim 28 is drawn to an isolated nucleic acid comprising a sequence encoding "a PLAG1 Protein", wherein the amino acid sequence of the PLAG1 protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116...or a fragment thereof which can be used to diagnose cells having a non-physiological proliferative capacity. Tommerup teaches these embodiments. (see pages 259-260 and 262, and SWISS-PROT sequence search result No. 4, which details that Tommerup teaches "a" PLAG1 protein or fragment thereof). Tommerup is considered to anticipate the claims because he teaches a cDNA encoding "a" PLAG1 protein and a fragment thereof, and teaches that these sequences can be

used in detecting malignant disorders (e.g., diagnose cells having a non-physiological proliferative capacity) (see page 259 and 264).

Regarding Claims 33-35, Tommerup teaches labeled cDNA comprising a sequence encoding "a PLAG1 Protein", wherein the amino acid sequence of the PLAG1 protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116...or a fragment thereof which can be used to diagnose cells having a non-physiological proliferative capacity. (see pages 260-261).

10. Claims 48 and 50-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Nollet et al. (Genomics (March 1996) 32: 413-424, previously cited).

Claims 48 and 50 are drawn to a macromolecules comprising a nucleic acid in isolated form, comprising a sequence encoding the promoter region of a CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity, wherein the nucleic acid is selected from the group consisting of "a" transcript corresponding to the nucleic acid, "a" cDNA corresponding to the nucleic acid, and "a" sense or antisense DNA corresponding to the nucleic acid. Nollet et al. discloses these embodiments (see pages 414-415 and pages 420-421).

Claims 51-52 are drawn to macromolecules comprising a nucleic acid in isolated form comprising at least one exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity, wherein the nucleic acid is selected from the group consisting of "a" transcript corresponding to the nucleic acid, "a" cDNA corresponding to the nucleic acid, and "a" sense or antisense DNA corresponding to the nucleic acid. Nollet et al. discloses these embodiments (see pages 414-415, 418 and pages 420-423).

Conclusion

11. No claims are allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
February 20, 2004

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